

Working Group on 2A Carcinogens

The Advisory Board on Toxic Substances and Workers Health

Update

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TASK: Should IARC Group 2A
Carcinogens be added to the SEM,
linking them to specific cancers?

Agents Classified by IARC

(International Agency for
Research on Cancer,
volumes 1-129)

Group 1: Carcinogenic to humans
121 agents

Group 2A: Probably carcinogenic to humans
89 agents

Group 2B: Possibly carcinogenic to humans
318 agents

Group 3: Not classifiable as to its
carcinogenicity in humans
499 agents

[Last update](#) March 26, 2021

Group 2A: Probably carcinogenic in humans

- *Limited* evidence of carcinogenicity in humans and *sufficient* evidence of carcinogenicity in experimental animals OR
- *Inadequate* evidence of carcinogenicity in humans and *sufficient* evidence of carcinogenicity in experimental animals and *strong* evidence that the carcinogenesis is mediated by a mechanism that also operates in humans OR
- *Limited* evidence of carcinogenicity in humans, but belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A

Selection of 2A Agents

- 22 agents updated as of 2016
- 18 of those 22 agents were toxic chemicals

Listing in 2020

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B5 1,3-Propane sultone

| | B | C | D | E | F |
|----|----------------------------------------------|-------|--------------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | Agent | Group | Volume | Year | Additional information |
| 2 | Pioglitazone | 2A | | 108 | 2016 |
| 3 | Polybrominated biphenyls | 2A | 41, Sup 7, 107 | | 2016 NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data, namely mechanistic similarity with polychlorinated biphenyls |
| 4 | Glyphosate | 2A | | 112 | 2017 |
| 5 | 1,3-Propane sultone | 2A | 4, Sup 7, 71, 110 | | 2017 NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data |
| 6 | Tetrafluoroethylene | 2A | 19, Sup 7, 71, 110 | | 2017 NB: Overall evaluation upgraded to Group 2A on the basis of sufficient evidence in experimental animals with a striking and atypical pattern of tumours |
| 7 | Malathion | 2A | 30, Sup 7, 112 | | 2017 |
| 8 | Diazinon | 2A | | 112 | 2017 NB: Overall evaluation upgraded to Group 2A based on mechanistic evidence |
| 9 | Silicon carbide whiskers | 2A | | 111 | 2017 |
| 10 | Dichloromethane (Methylene chloride) | 2A | Sup 7, 71, 110 | | 2017 |
| 11 | DDT (4,4'-dichlorodiphenyltrichloroethane) | 2A | Sup 7, 53, 113 | | 2018 |
| 12 | Red meat (consumption of) | 2A | | 114 | 2018 |
| 13 | 2-Mercaptobenzothiazole | 2A | | 115 | 2018 |
| 14 | Hydrazine | 2A | 4, Sup 7, 71, 115 | | 2018 |
| 15 | N,N-Dimethylformamide | 2A | 47, 71, 115 | | 2018 |
| 16 | Tetrabromobisphenol A | 2A | | 115 | 2018 |
| 17 | Very hot beverages at above 65 °C (drinking) | 2A | | 116 | 2018 online |
| 18 | Styrene | 2A | 60, 82, 121 | | 2019 |
| 19 | 3,3',4,4'-Tetrachloroazobenzene | 2A | | 117 | 2019 NB: Overall evaluation upgraded to Group 2A |
| 20 | Dieldrin, and aldrin metabolized to dieldrin | 2A | 5, Sup 7, 117 | | 2019 2-Mercaptobenzothiazole (MBT) is an industrial chemical that is used principally in the manufacture of rubber. |
| 21 | Styrene-7,8-oxide | 2A | Sup 7, 60, 121 | | 2019 NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data |
| 22 | Night shift work | 2A | 98, 124 | In prep. | NB: Volume 98 evaluated shiftwork that involves circadian disruption |
| 23 | Glycidyl methacrylate | 2A | | 125 | In prep. |
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Selection of 2A Agents –Tasks of the Working Group 2021

- 22 agents updated as of 2016
- 18 of those 22 agents were toxic chemicals
- Which should be included in the SEM?

IARC revised approach -Preamble

- Systematic Review
- Synthesis of data
- Evidence of Cancer in Humans, Evidence of Cancer in Animals, Mechanistic Evidence, Evaluation
- https://monographs.iarc.who.int/wp-content/uploads/2019/07/2019-SR-001-Revised_Preamble.pdf

| Evidence of Cancer in Humans | Evidence of Cancer in Experimental Animals | Mechanistic Evidence | Evaluation |
|------------------------------|--------------------------------------------|----------------------------------------|-----------------------------------------|
| Sufficient | | | Carcinogenic (Group 1) |
| | Sufficient | Strong (exposed humans) | |
| Limited | Sufficient | | Probably carcinogenic (Group 2A) |
| Limited | | Strong | |
| | Sufficient | Strong (human cells or tissues) | |
| | | Strong (mechanistic class) | |
| Limited | | | Possibly carcinogenic (Group 2B) |
| | Sufficient | | |
| | | Strong (experimental systems) | |
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https://monographs.iarc.fr/wp-content/uploads/2019/07/2019-SR-001-Revised_Preamble.pdf

Working Group Approach 2021

- Review of 18 toxic substances –relying predominately on IARC monographs
- Consider for selection of 2A carcinogens to be included in SEM, those with at least *limited evidence of cancer in humans*.
- 11/18 had limited evidence of human cancers in specific organs (See Tables)
- All 11 were found in the SEM, but none had any linkages to the human cancer sites identified in the IARC review
- Of the cancers listed in the “Human Health Effects” of SEM, none of the Group A carcinogens was listed under those organs
- Breast, prostate and testicular cancers were not listed at all in the SEM. (Only diseases covered by Part E are displayed in SEM)

Table 1: Group 2A Carcinogens with Limited evidence in humans for cancers

| 2A Carcinogen | Description | Associated Cancers | SEM Status |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Glyphosate ("Roundup") | Herbicide-widely used | Non-Hodgkin Lymphoma | Present in SEM No Diseases (or cancers) listed in Haz-Map |
| Malathion | Organophosphate insecticide | Non-Hodgkin Lymphoma; Cancer of the Prostate | Present in SEM No associated cancers listed Not listed under Lymphoma, Non-Hodgkin |
| Diazinon | Organophosphate insecticide, miticide, and nematicide | Non-Hodgkin Lymphoma Leukemia Cancer of the Lung | Present in SEM as Haz-Map name: O,O-Diethyl-O-(2-isopropyl- 4-methyl-6-pyrimidinyl) phosphorothioate No associated Cancers listed |
| Dichloromethane (Methylene Chloride) | Solvent | Biliary-Tract Cancer Non-Hodgkin Lymphoma | Present in SEM No associated cancers listed |
| DDT 4,4'-dichlorodiphenyltrichloro- ethane | Insecticide | Liver Cancer Testicular Cancer Non-Hodgkin Lymphoma | Present in SEM No associated cancer listed Not listed under Liver, Lymphoma-Non-Hodgkin; no testicular |
| 2-Mercaptobenzothiazole | Organosulfur compound used in the sulfur vulcanization of rubber | Urinary bladder cancer | Present in SEM No associated cancer listed Not listed under Bladder Cancer |
| Hydrazine | Used in polymerization; precursor to pesticides and pharmaceuticals, other reactions | Lung Cancer | Present in SEM No associated cancer listed Not listed under Lung Cancer |

Table 1: Group 2A Carcinogens with Limited evidence in humans for cancers

| | | | |
|-----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| N, N-Dimethylformamide | Solvent (used in mfg fo polyacrylonitirele fibers, polyurethane and polamide coatings, electronics, other) | Testicular Cancer | Present in SEM No associated cancer listed |
| Styrene | | Lymphohaematopoietic malignancies (stronger and more consistent for AML and T-cell lymphoma) | Present in SEM No associated Cancer listed Styrene not listed under leukemia, lymphoma, or Lung cancer |
| Aldrin and its metabolite dieldrin [Inadequate evidence for aldrin, but limited evidence for its metabolite dieldrin] | Synthetic organochlorine pesticides | Cancer of the Breast | Present in SEM No associated Cancer listed in Haz-Map Breast Cancer not listed in SEM |
| Silicon Carbide “Whiskers” | “Silicon carbide whiskers are monocrystalline and homogeneous in form, while fibrous silicon carbide is mostly polycrystalline and heterogeneous in form”. Given differences in physiochemical properties- Separate evaluation for “fibers” and “whiskers” | Lung Cancer | Present in SEM No associated Cancer listed Not listed under Lung Cancer |

Table 2: Cancers and Group 2A Carcinogens To Be Added to SEM

| CANCER TYPE | 2A Carcinogen* |
|------------------------------------|--------------------------------------------------------------------------|
| Lung Cancer | Hydrazine Diazinon Silicon Carbide “Whiskers” |
| Lymphoma, Non Hodgkin | DDT Diazinon Dichloromethane Glyphosate Malathion Styrene |
| Leukemia | Diazinon |
| Lymphohaematopoietic | Styrene |
| Testicular Cancer (need to add) | DDT N, N-Dimethylformamide |
| Bladder Cancer | 2-Mercaptobenzothiazole |
| Breast Cancer (need to add) | Dieldrin (metabolite of Aldrin) |
| Liver Cancer | DDT |
| Biliary Tract Cancer | Dichloromethane |

RECOMMENDATIONS

- Toxic substances that are found to be probable human carcinogens (IARC Group 2A) and that have limited human epidemiological evidence for specific human cancer sites as identified in table 1, should be linked to those cancer sites in the SEM.
- The SEM should specify that IARC and NTP evaluations have been used in addition to HAZ MAP for the purpose of asserting linkages between toxic substances and human cancer sites.
- Future IARC Group 2A substance-cancer linkages identified by IARC or NTP should be incorporated in the SEM. Data from IARC and NTP should be used in addition to HAZ MAP for health effects and linkages of toxic substances to cancers.